APPENDIX B

Data Sources

NOTE: Before using these P2 Framework Models, or any screening level model, a thorough search for measured data should be conducted. Measured data should be used if available instead of estimated (predicted) data because estimation methods, such as these screening models, contain inherent uncertainties.

The data sources included here are not intended to represent the only or best sources of data available. Readers are strongly encouraged to conduct their own searches for data.

The URLs of certain Internet sites are provided here to provide information to users of the manual. Users are cautioned that due to the dynamic nature of the Internet, these URLs may have been changed from the time of the writing of this document. In case a URL is no longer correct, the user is advised to use any of the search engines to locate the correct URL.

Types of Data Sources included here are:

1. Physical / Chemical Property Data
2. Chemical Human Hazard Data
3. Chemical Environmental Hazard Data
4. Environmental Release Data
5. Exposure Parameter and Population Data

APPENDIX B: Data Sources

Physical / Chemical Property and Fate Data Sources

Beilstein Online http://www.beilstein.com/products/online/online.shtml provides access to data on organic compounds. With about 8 million heterocyclic, acyclic and isocyclic compounds, the Beilstein database covers the literature from 1771 onwards. Also available through www.cas.org/ONLINE/DBSS/beilsteinss.html.

BIODEG http://esc.syrres.com/EFDBInfo.htm contains experimental values as in CHEMFATE, but only relating to biodegradation subjects. In addition, BIODEG contains evaluation codes that can be used for structure/biodegradability correlations. This file contains over 5,800 records of actual experimental results on biodegradation studies for approximately 800 chemicals. Experimental details, such as chemical concentration and rate of degradation, are included.

BIOLOG http://esc.syrres.com/EFDBInfo.htm or the Microbial Degradation/Toxicity File, provides sources of microbial toxicity and biodegradation data. It is is more detailed than DATALOG, but does not include experimental values. BIOLOG contains 70,000 records on 8,150 chemicals.

CHEMFATE http://esc.syrres.com/EFDBInfo.htm is a data value file with 25 categories of environmental fate and physical/chemical property data on commercially important chemical compounds. Actual experimental values (rate constants, experimental conditions, physical properties, etc.) are abstracted and retained in the file. CHEMFATE contains 17,260 records on 1,728 chemicals. Recommended physical property values were collected for the SARA Section 313 TRI chemicals.

ChemFinder http://chemfinder.cambridgesoft.com/ online searching by CAS RN or chemical name includes reference databases including The Merck Index, Chemical, Reaction, and Safety databases.

CRC Handbook of Chemistry and Physics www.crcpress.com CRC Handbook of Chemistry and Physics on CD ROM, Version 2003 ISBN: 0849315565

CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data, 78th Edition, 1997. David R. Lide (Editor). CRC Press; ISBN: 0849304784. Handbook contains CAS Registry numbers, and chemical and physical properties.

DATALOG http://esc.syrres.com/EFDBInfo.htm is a bibliographic file indexed by Chemical Abstract Service (CAS) registry number that contains eighteen types of environmental fate data. Since individual articles require only cursory examination, no experimental values are entered into the file, and thus, large numbers of chemicals can be rapidly incorporated. This file is the largest in the EFDB, containing 380,000 records on over 16,800 chemicals. DATALOG indicates where environmental fate and exposure data can be found by searching for 18 different properties.

EFHB (Environmental Fate Data Base) http://esc.syrres.com/EFDBInfo.htmThe EFDB is comprised of several interrelated files, DATALOG, CHEMFATE, BIOLOG, and BIODEG. These databases share a CAS RN file containing over 20,000 chemicals with preferred name and formula, and a bibliographic file containing full references on over 36,000 articles cited.

Envirofate contains data on approximately 800 chemicals. Envirofate contains summary information concerning the environmental fate and the physical-chemical properties of chemicals released into the environment. Chemicals selected for inclusion in the database are produced annually in excess of one million pounds. ENVIROFATE contains twenty-four types of data extracted from papers published worldwide dealing with environmental fate and behavior studies. It is available through CIS (Chemical Information System) www.nisc.com/cis/ (fee).

APPENDIX B: Data Sources

Physical / Chemical Property and Fate Data Sources (continued)

Gmelin Handbook of Inorganic and Organometallic Chemistry
http://www.beilstein.com/products/xfire/gmelin.shtml covers organometallic & inorganic compounds. The Gmelin database covers more than 1.4 million organometallic and inorganic compounds (including coordination compounds, alloys, glasses, ceramics, polymers and minerals), with more than 800 property fields defined.

Handbook of Environmental Fate and Exposure Data for Organic Chemicals. 1997. P.H. Howard (ed.) Vol V. Solvents III. SRC Handbooks Series. CRC/Lewis Publishers, Boca Raton, FL.

Handbook of Environmental Fate and Exposure Data for Organic Chemicals. 1992. P.H. Howard (ed.) Vol IV. Solvents II. SRC Handbooks Series. Lewis Publishers, Chelsea, MI.

Handbook of Physical Properties of Organic Chemicals. PHYSPROP. Howard, P.H.; Meylan, W.M. 1997. CRC/Lewis Publishers, Boca Raton, FL. There is also a database version.

Handbook of Property Estimation Methods for Chemicals. 2000. Boethling, R.S. and MacKay, D. Environmental Health Sciences. Lewis Publishers. Washington, D.C.

Handbook of Environmental Fate and Exposure Data for Organic Chemicals. 1990. P.H. Howard (ed.) Vol II. Solvents. SRC Handbooks Series. Lewis Publishers, Chelsea, MI.

Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, 1990. Warren J. Lyman, William F. Reehl, and David H. Rosenblatt. American Chemical Society; ISBN: 0841217610. Contains methods for estimating density, vapor pressure, water solubility, and other chemical properties relevant to environmental fate.

Handbook of Environmental Data on Organic Chemicals, 3rd Edition, 1997. Karel Verschueren (Editor). John Wiley & Sons; ISBN: 0471286591. An extensive text compiling information on organic products. The data given include physical properties; e.g., formula, physical appearance, molecular weight, melting point, boiling point, vapor pressure, and solubility.

Handbook of Environmental Degradation Rates. Howard, P.H.; Boethling, R.S.; Jarvis, W.F.; and Meylan, W. 1991. New York: Lewis Publishers, Inc. ISBN: 0873713583.

Handbook of Environmental Fate and Exposure Data for Organic Chemicals. 1989. P.H. Howard (ed.) Vol I. Large Production and Priority Pollutants. SRC Handbooks Series. Lewis Publishers, Chelsea, MI.

Handbook of Environmental Fate and Exposure Data for Organic Chemicals. 1991. P.H. Howard (ed.) Vol III. Pesticides. SRC Handbooks Series. Lewis Publishers, Chelsea, MI.

Hawley's Condensed Chemical Dictionary, 13th Edition, 1997. Gessner Goodrich Hawley (Editor), and Richard J., Sr. Lewis (Editor). John Wiley & Sons; ISBN: 0471292052. (A CD-ROM version is also available). A compendium of technical data and descriptive information covering many thousand chemicals, including their industrial uses, and trademark names.

Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals: Volume V– Pesticide Chemicals, by Donald Mackay, Wan-Ying Shiu, Kuo-Ching Ma. Boca Raton, FL, Lewis Publishers, 1997. 812p., bibliog., index. ISBN 1-56670-255-0.

APPENDIX B: Data Sources

Physical / Chemical Property and Fate Data Sources (continued)

Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals. Vol I and II. 1992. MacKay, D.; Shiu, W.Y; and Kuo, C.M. Lewis Publishers. New York.

Kirk-Othmer Concise Encyclopedia of Chemical Technology, 3rd Edition, 1989. Martin Grayson (Contributor), Herman F. Mark, and Donald F. Othmer. John Wiley & Sons; ISBM: 0471517003. Provides a concise yet comprehensive summary of various topics in applied aspects of chemistry & chemical engineering. It emphasizes the application of chemistry and chemical engineering to industrially important concepts, products, processes and uses. It provides references for further reading on each of these topics. http://www.mrw.interscience.wiley.com/kirk/

Lange's Handbook of Chemistry. 15th Edition. McGraw-Hill, 1999. Known Lange's Handbook, this classic reference covers the entire field of chemistry.

Merck Index: An Encyclopedia of Chemicals, Drugs, & Biologicals by M.J. O'Neil (Editor), et al Publisher: Merck & Co; ISBN: 0911910131; 13th edition (October 2001). A one-volume encyclopedia of chemicals, drugs and biologicals. Contains basic property data such as molecular weight, physical and toxicity data, chemical structures, and commercial uses.

Merck Index 13th CD-ROM Edition http://products.camsoft.com/ProdInfo.cfm?pid=231 This stand-alone edition contains all the information in The Merck Index 13th Edition.

APPENDIX B: Data Sources

Chemical Human Hazard Data Sources

Agency for Toxic Substances and Disease Registry (ATSDR) www.atsdr.cdc.gov/toxpro2.html contains toxicological profiles of hazardous chemicals most often found at facilities on CERCLA's National Priority List.

CAS (Chemical Abstracts Service) http://www.cas.org a division of the American Chemical Society, provides fee-based online access to databases of chemical information. A useful method of searching is through CAS's Science and Technology Network (STN) that searches numerous databases of chemical information.

CCRIS http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?CCRIS Chemical Carcinogenesis Research Information System contains carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition data provided by the National Cancer Institute (NCI).

CHEMEST http://www.agnic.nal.usda.gov/agdb/chemest.html contains data for estimating the properties and chemicals of environmental concern. Available through Technical Database Services, Inc.

CHEMFATE http://esc.syrres.com/efdb/Chemfate.htm contains evaluated physical property values, rate constants and monitoring concentrations for approximately 1,730 commercially significant compounds.

ChemFinder http://chemfinder.cambridgesoft.com/ contains synonyms, structure, and physical chemical properties and a link to measured data from Merck Index.

Chemical Categories Document http://www.epa.gov/opptintr/newchems/chemcat.htm Developed under the New Chemicals Program within EPA's Office of Prevention, Pesticides, and Toxic Substances (OPPT), includes summaries of chemical categories developed to facilitate the review process of new chemicals (Premanufacture Notices) under TSCA Section 5. It is not intended to be a comprehensive list of all chemical substances. EPA's PBT Profiler screening model www.pbtprofiler.net also searches the structure of the chemical entered and identifies any structures present in the chemical that are described in the Chemical Categories Document.

CHEMID - Contains chemical names, synonyms, molecular formulas and CAS numbers. Available through Internet Grateful Med at http://igm.nlm.nih.gov/

ChemIDplus http://chem.sis.nlm.nih.gov/chemidplus/setupenv.html This software allows for viewing and searching the NLM databases by numerous chemical synonyms, structures, regulatory list information, and contains links to other databases containing information about the chemicals. Using ChemIDplus and ISIS/Draw www.mdl.com/products/isisdraw.html databases searches can be conducted by name, CAS Registry Number, or by structure and substructure. Of the 350,000 records, about one-third have identified structures in the record. Using the (sub)structure searching, non-cancer health effects for structural analogues to the chemical(s) of concern can be identified.

DART/ETIC (Developmental and Reproductive Toxicology and Environmental Teratology) Information Center http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?DARTETIC Contains current and older literature on developmental and reproductive toxicology.

EMIC (Environmental Mutagen Information Center) http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?EMIC contains mutagenicity data.

APPENDIX B: Data Sources

Chemical Human Hazard Data Sources (continued)

GENE-TOX http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?GENETOX GENE-TOX contains peer-reviewed mutagenicity test data from the U.S. EPA.

Health Effects Assessment Summary Tables (HEAST). 1997. U.S. EPA. Contains RfD, RfC, unit risk, and slope factor values for selected chemicals. Available through the National Technical Information Service (NTIS) www.ntis.gov Doc. Number OERR 9200.6-303 (97-1).

Health Assessment Documents (HAD) U.S. EPA. Reviews health effects of specific chemicals.

HSDB - Hazardous Substance Databank http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?HSDB This is an on-line database containing scientifically peer-reviewed data on a chemical properties and fate, human, animal and environmental toxicity, environmental fate, regulations, and treatments. This database is available through TOXNET at http://toxnet.nlm.nih.gov; through STN International at www.cas.org/stn.html; and through CCINFOweb at http://ccinfoweb.ccohs.ca/

IRIS http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?IRIS Integrated Risk Information System contains data used by the U.S. EPA in support of human health risk assessment, focusing on hazard identification and dose-response assessment.

IRIS (Integrated Risk Information System). U.S. EPA. Reviews studies used in the derivation of RfD, RfC, unit risk, and slope factor values. A web prototype is available on the Internet at www.epa.gov/ngispgm3/iris

IUCLID http://ecb.jrc.it/existing_chemicals/ International Uniform Chemical Information Database (IUCLID) is the basic tool for data collection and evaluation within the EU-Risk Assessment Programme. IUCLID contains CAS RN, physical / chemical data, toxicology, environmental toxicity and fate information on HPV Chemicals.

MEDLINE is a database of over 11 million article references published in more than 4300 biomedical journals and magazines, and can be searched for free using NLM's PubMed search system. http://medlineplus.gov

MEDLINEplus contains pages of carefully selected links to Web resources with authoritative health information, including dictionaries, directories, organizations, news sources and 400 health topics. http://medlineplus.gov/

National Library of Medicine Online Data Sources. A very useful online source of health effects data is the National Library of Medicine web site, which has many databases that can be searched through TOXNET http://toxnet.nlm.nih.gov/

National Institute of Occupational Safety and Health (NIOSH). Presents Health Hazard Evaluations and Industry-wide Studies. Contains literature reviews of occupational exposure data, health effects data, and animal studies. Rationale are presented for the derivation of NIOSH exposure levels. www.cdc.gov/niosh/homepage.html

National Institute of Occupational Safety and Health (NIOSH) www.cdc.gov/niosh/homepage.html presents health hazard evaluations and industry-wide studies. Contains literature reviews of occupational exposure data, health effects data, and animal studies. Rationale are presented for the derivation of NIOSH exposure levels.

APPENDIX B: Data Sources

Chemical Human Hazard Data Sources (continued)

NLM Gateway (http://gateway.nlm.nih.gov/gw/Cmd another useful source on the NLM's web site, allows users to search NLM databases using multiple retrieval systems. As of June 2002 Gateway searches MEDLINE, PubMed, and MEDLINEplus.

Patty's Industrial Hygiene and Toxicology, Vols. 1-4. John Wiley & Sons. (CD-ROM version is available). Contains toxicology and properties of selected industrial chemicals and classes of chemicals.

PHYSPROP - The Physical Properties Database (PHYSPROP) contains chemical structures, names and physical properties for over 25,070 chemicals. This information is available at the Syracuse Research Corporation (SRC) web site at http://escplaza.syrres.com/interkow/PhysProp.htm

PubMed is a Web-based search system, produced by NLM's National Center for Biotechnology Information (NCBI), which allows users to access a superset of NLM's MEDLINE database containing MEDLINE, in-process citations and articles from selectively indexed journals that normally would not be selected for MEDLINE indexing. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

STN International www.cas.org/stn.html and CCINFOweb http://ccinfoweb.ccohs.ca/aboutCCINFOWeb.html contain information on chemical abstracts, CAS numbers, molecular formulas, reaction information, chemical indexing,etc.

TOXLINE http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?TOXLINE Contains an extensive array of references to literature on biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals.

TSCATS. Provides public assess to information submitted to U.S. EPA under the various sections of TSCA (Toxic Substances Control Act). TSCATS is available from several on-line sources (CIS, NLM) or on the Internet at www.rtk.net/www/data/tsc_all.html or http://esc.syrres.com/efdb/TSCATS.htm

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Chemical Environmental Hazard Data Sources

Acute Toxicity of Organic Chemicals to Fathead Minnows (Pimephales promelas), Vols. 1-5. Brooke, L.T., D.J. Call, D.L. Geiger and C.E. Northcott, Eds. 1984-1990. This is a comprehensive source of measured fish toxicity values for a single species (fathead minnows), including fish LC50 data.

Ambient Water Quality Criteria Documents. U.S. EPA. Contains aquatic toxicity values chemicals for which ambient water quality criteria have been developed, and is useful for organic and inorganic compounds. www.epa.gov/waterscience/pc/ambient.html

AQUIRE (Aquatic Information Retrieval) - Contains data extracted from published literature worldwide and from independently compiled data files; includes data on acute and chronic toxicity, bioaccumulation, and sublethal effects data from tests performed on freshwater and saltwater species. AQUIRE is accessible through CIS (Chemical Information System), EPA's Office of Research and Development; and the entire AQUIRE database can be downloaded from www.epa.gov/medecotx/data_download/aquire/aquire_ascii_download.htm

ChemID - Maintained by the National Library of Medicine (NLM); serves as an authority file for the identification of chemical substances cited in NLM databases. Contains chemical names, synonyms, molecular formulas and CAS numbers. Available through Internet Grateful Med at http://igm.nlm.nih.gov/

CIS (Chemical Information System) www.nisc.com/cis/ (fee) - 30 databases concerned with chemicals having an environmental impact or that are regulated in some way. Originally developed by the National Institutes of Health and EPA for managing chemical data and information, CIS is now owned by Oxford Molecular.

CTA (Catalog of Teratogenic Agents) - Emphasizes human data and covers pharmaceuticals, chemicals, environmental pollutants, food additives, household products, and viruses; substances are listed alphabetically, and each entry briefly summarizes research procedures and results. The Catalog is accessible as a database through CIS (Chemical Information System) www.nisc.com/cis/ (fee)

CCRIS (Chemical Carcinogenesis Research Information System) - Contains data derived from carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition studies; contains over 8,000 chemical records and is sponsored by the National Cancer Institute. The database is available through CIS (Chemical Information System) and the National Library of Medicine's TOXNET system. www.nlm.nih.gov/pubs/factsheets/ccrisfs.htm

DART (Development and Reproductive Toxicology) http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?DARTETIC and ETICBACK (Environmental Teratology Information Center Backfile) - DART is a bibliographic database covering literature on teratology and other aspects of developmental toxicology. It is managed by NLM and funded by EPA, the National Institute of Environmental Health Sciences (NIEHS), and the National Center for Toxicological Research of the Food and Drug Administration. DART is a continuation of ETICBACK, which contains 49,000 citations to teratology literature published from 1950-1989.

DATALOG - Contains citations for published articles containing data on the environmental fate and the physical-chemical properties of chemicals released into the environment. Available through CIS (Chemical Information System) www.nisc.com/cis/ (fee)

APPENDIX B: Data Sources

Chemical Environmental Hazard Data Sources (continued)

EMIC (Environmental Mutagen Information Center) http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?EMIC and EMICBACK (Environmental Mutagen Information Center Backfile) - EMIC is a bibliographic database containing some 20,000 citations to literature on chemical, biological, and physical agents that have been tested for genotoxic activity. It is produced by the Oak Ridge National Laboratory (ORNL) and funded by EPA and NIEHS. EMIC covers literature published since 1991. EMICBACK contains over 75,000 citations to literature published from 1950-1990.

Envirofate - Contains summary information from papers published worldwide on the environmental fate and the physical-chemical properties of chemicals released into the environment; chemicals included are those produced annually in excess of one million pounds; available through CIS (Chemical Information System) www.nisc.com/cis/ (fee)

GENE-TOX (Genetic Toxicology) http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?GENETOX GENE-TOX Contains genetic toxicology test results on over 3,000 chemicals. Selected mutagenicity assay systems and the source literature are reviewed by work panels of scientific experts for each of the test systems under evaluation. The GENE-TOX data bank is the product of these data review activities. Each test system in GENE-TOX has been peer reviewed and is referenced.

Handbook of Environmental Data on Organic Chemicals, 3rd Edition, 1997. Karel Verschueren (Editor). John Wiley & Sons; ISBN: 0471286591. An extensive text compiling information of organic products. The data given include physical properties: e.g., formula, physical appearance, molecular weight, melting point, boiling point, vapor pressure, and solubility.

HSDB (Hazardous Substances Data Bank) http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?HSDB [Discussed in “Physical / Chemical Property And Fate Data Sources”]

IRIS (Integrated Risk Information System) http://www.epa.gov/iris Prepared and maintained by EPA, IRIS is an electronic database containing health risk and EPA regulatory information on specific chemicals. IRIS was developed by EPA staff in response to a growing demand for consistent risk information on chemicals substances for use in decision-making and regulatory activities. IRIS is designed for EPA staff, but is also accessible to state and local environmental health agencies. The information in IRIS is intended for EPA staff with extensive training in toxicology, but with some knowledge of health sciences. The database can also be searched online through the TOXNET system. List of IRIS Substances at http://www.epa.gov/docs/ngispgm3/iris/subst/index.html

Merck Index - Encyclopedia of chemicals, drugs, pesticides, and biologically active substances; is available in both print and electronic versions. The online database, which is available through CIS (Chemical Information System) and DIALOG, contains nearly 10,000 records containing references to approximately 30,000 substances, inclusive dates late 19th century to present, updated semi-annually, produced by Merck & Co., Inc.

NIOSH (National Institute for Occupational Safety and Health) - established by the Occupational Safety and Health Act of 1970; is part of the Centers for Disease Control and Prevention (CDC); is the only federal Institute responsible for conducting research and making recommendations for the prevention of work-related illnesses and injuries. NIOSHTIC and RTECS are both produced by NIOSH. http://www.cdc.gov/niosh/homepage.html

APPENDIX B: Data Sources

Chemical Environmental Hazard Data Sources (continued)

NIOSHTIC - the National Institute for Occupational Safety and Health's (NIOSH) electronic, bibliographic database of literature in the field of occupational safety and health. NIOSHTIC is updated quarterly and is available online and on compact disk from several vendors. Information contained within NIOSHTIC is selected from a number of sources. NIOSHTIC is accessible as a subfile in the TOXLINE database. http://www.cdc.gov/niosh/nioshtic.html#NTIC4

NLM (National Library of Medicine) http://sis.nlm.nih.gov/ One of the national libraries of the United States, located on the campus of the National Institutes of Health, it provides a number of services and resources for use by the American public. Fact sheets on NLM's toxicological databases are at http://sis.nlm.nih.gov/tox_chart.htm

NTP (National Toxicology Program) conducts toxicity/carcinogenesis studies on agents suspected of posing hazards to human health; data on more than 800 chemical studies are on file. NTP Information is routinely provided to industry and the public on an as requested basis. National Toxicology Program Technical Reports at http://ehis.niehs.nih.gov/ntp/docs/ntp.html (fee). The National Toxicology Program Web site is http://ntp_server.niehs.nih.gov/Main_Pages/Chem_HS.html NIEHS Environmental Health Information Service (EHIS) is http://ehis.niehs.nih.gov/ntp/docs/chem_hs.html (fee)

PHYTOTOX - Contains data from the open literature on the effects of the application of one concentration of a single organic chemical on a particular terrestrial vascular plant species. Phytotox is available through CIS (Chemical Information System) www.nisc.com/cis/, as well as through EPA's Office of Research and Development.

RTECS (Registry of Toxic Effects of Chemical Substances) - Contains over 100,000 records covering 1971 to present, quarterly updates, maintained by NIOSH; is a comprehensive database of toxic effects and general toxicology reviews, data on skin and/or eye irritation, mutation, reproductive consequences, and tumorigenicity are provided. Toxic effects are linked to literature citation from both published and unpublished government reports (including unpublished test data from TSCATS, the EPA TSCA test submissions database), and published articles from the scientific literature. RTECS database is available from a number of vendors and can be accessed via the TOXNET at http://toxnet.nlm.nih.gov

SANSS GREENCARD (Structure and Nomenclature Search System) - www.nisc.com/cis/details/sanss.htm contains records for more than 500,000 chemicals, is an index to most of the other CIS (Chemical Information System) www.nisc.com/cis/ Components/databases as well as to over 100 other important sources of information on environmentally significant chemicals; is a pointer to CIS sources such as RTECS, the Merck Index, and AQUIRE, as well as non-CIS sources such as IARC Monographs, Hazardous Substances Data Bank, and National Toxicology Program studies.

Subchronic Toxicity of Industrial and Agricultural Chemicals to Fathead Minnows (Pimephales promelas), Volume 1. S Call, D.J. and D.L. Geiger, Eds. 1992. source of measured fish toxicity values for a single species (fathead minnows), including fish EC50 data.

Toxicity of Power Plant Chemicals to Aquatic Life. 1973. Presents aquatic toxicity values for organic and inorganic chemicals used by power plant. U.S. Atomic Energy Commission.

APPENDIX B: Data Sources

Chemical Environmental Hazard Data Sources (continued)

TOXLINE http://toxnet.nlm.nih.gov/cgi_bin/sis/htmlgen?TOXLINE the National Library of Medicine's extensive collection of online bibliographic information covering the biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals. TOXLINE and its backfile TOXLINE65 together contain more than 2.5 million bibliographic citations, almost all with abstracts and/or indexing terms and CAS Registry Numbers. The information in TOXLINE is taken from secondary sources which formulate the subfiles listed below. Citations with publication year 1980 and older are located in the backfiles.

TOXNET (TOXicology Data NETwork) is a computerized system of files oriented to toxicology and related areas. It is managed by the National Library of Medicine's (NLM) Toxicology and Environmental Health Information Program (TEHIP) and runs on Sun servers in a UNIX-based environment. http://toxnet.nlm.nih.gov TOXNET Web interface also allows users to search for toxicology data in the following toxicology data files: Hazardous Substances Data Bank, Chemical Carcinogenesis Research Information System, Integrated Risk Information System, and GENE-TOX, as well as EPA's Toxics Release Inventory (TRI).

TSCATS (Toxic Substances Control Act Test Submissions) - Data submitted by industry to EPA under several provisions of the Toxic Substances Control Act, TSCATS database indexes these submissions, which include unpublished health and safety studies, chemical test data, and substantial risk data submitted to EPA under TSCA sections 4, 8(d), 8(e), and FYI. The actual studies can be purchased from the National Technical Information Service (NTIS) for a fee and CIS (Chemical Information System). TSCATS is available from several on-line sources (CIS, NLM), on the Internet at www.rtk.net/www/data/tsc_all.html or http://esc.syrres.com/efdb/TSCATS.htm TSCATS can be viewed on microfiche in the TSCA Non-Confidential Information Center (the TSCA Docket).

APPENDIX B: Data Sources

Environmental Release Data Sources

AQS (The Air Quality System) database http://www.epa.gov/air/data/aqsdb.html contains measurements of "criteria air pollutant" concentrations in the 50 United States, plus the District of Columbia, Puerto Rico, and the Virgin Islands.

Chemical Engineering Branch Manual for the Preparation of Engineering Assessments. 1991. U.S. EPA. Conducted by IT Environmental Programs for Office of Toxic Substances (OTS) under Contract No. 68-D8-0112. Washington D.C.

ISDB (Industry Studies Database). U.S. EPA. Contains survey data collected by the Office of Solid Waste (OSW) covering both RCRA and non-RCRA wastes generated by 470 facilities in 11 industries. The data include company identify and location, SIC code, product name, production volume, waste stream properties and category, constituents and their concentrations in the waste stream, management practice and location, and quantity of waste stream.

Kirk-Othmer Concise Encyclopedia of Chemical Technology, 3rd Edition, 1989. Martin Grayson (Contributor), Herman F. Mark, and Donald F. Othmer. John Wiley & Sons; ISBN: 0471517003. This is a comprehensive source of chemical synthesis processes.
http://www.mrw.interscience.wiley.com/kirk/

Office of Water Effluent Limitations Guidelines and Standards (for selected industries).
http://cfpub.epa.gov/npdes/techbasedpermitting/effguide.cfm

PCS (The Permit Compliance System) is an information management system maintained by the U.S. EPA's Office of Wastewater Enforcement and Compliance (OWEC), to track the permit, compliance, and enforcement status of facilities regulated by the National Pollutant Discharge Elimination System (NPDES). PCS tracks information about wastewater treatment, industrial, and Federal facilities discharging into navigable waters. http:/www.epa.gov/enviro/ or
http://www.epa.gov/enviro/html/pcs/pcs_overview.html#PCS

TRI (Toxic Chemical Release Inventory) Files - TRI contains information on the annual estimated releases of toxic chemicals to the environment. It is mandated by the Emergency Planning and Community Right-to-Know Act and is based upon data submitted to the Environmental Protection Agency (EPA) from industrial facilities throughout the U.S.A. This data includes names and addresses of the facilities, and the amounts of certain toxic chemicals they release to the air, water, or land, or transfer to waste sites. Information is included on over 600 chemicals and chemical categories. Separate TRI files are available for each year beginning with 1987. Since 1991, pollution prevention data are also reported by each facility for each chemical. http:/www.epa.gov/enviro/ or
http://www.epa.gov/tri/

Published chemical monitoring data reports.

Company product literature.

APPENDIX B: Data Sources

Exposure Parameter Data Sources

Exposure Factors Handbook. 1996. Exposure Factors Handbook: V.I General Factors EPA/600/P-95/002Ba; V.II Food Ingestion Factors EPA/600-P-95/002Bb; V.III Activity Factors EPA/600/P-95-002Bc August 1996. U.S. EPA. Presents a summary of available data on human behaviors and characteristics which affect exposure to environmental contaminants and presents recommended values to use for these factors. It provides factor data on ingestion rates of foods, water, breast milk, and soil; factors for inhalation and dermal exposure; data for body weight, lifetime, activity factors; data for use of consumer products; and data for exposures that occur in residences. Available in pdf format at www.epa.gov/ORD/WebPubs/exposure/

Methods for Assessing Exposure to Chemical Substances. U.S. EPA. 1985. Office of Toxic Substances (OTS). Prepared by Versar, Inc. under EPA Contract No. 68-01-6271. Washington DC. These methods described in these volumes were identified by OTS (now officially OPPT) as having utility in exposure assessments on existing and new chemicals under the OTS program. The title of the basic volumes are as follows*:

V. 1. Methods for Assessing Exposure to Chemical Substances. (EPA 560/5-85-001).
V. 2. Methods for Assessing Exposure to Chemical Substances in the Ambient Environment. (EPA 560/5-85-002).
V. 3. Methods for Assessing Exposure from Disposal of Chemical Substances (EPA 560/5-85-003).
V. 4. Methods for Enumerating and Characterizing Populations Exposed to Chemical Substances (EPA 560/5-85-003).
V. 5. Methods for Assessing Exposure to Chemical Substances in Drinking Water (EPA 560/5-85-005).
V. 6. Methods for Assessing Occupational Exposure to Chemical Substances (EPA 560/5-85-006).
V. 7. Methods for Assessing Consumer Exposure to Chemical Substances (EPA 560/5-85-007).
V. 8. Methods for Assessing Environmental Pathways of Food Contamination (EPA 560/5-85-008).
V. 9. Methods for Assessing Exposure to Chemical Substances Resulting from Transportation-Related Spills (EPA 560/5-85-009).
V. 11. Methods for Estimating the Migration of Chemical Substances from Solid Matrices (EPA 560/5-85-015).
V. 13. Methods for Estimating Retention of Liquids on Hands (EPA 560/55-85-017).
*Volumes 10 and 12 were not issued.

Population Data Sources

Census of Population Reports. U.S. Bureau of the Census. Available from the U.S. Bureau of the Census on CD-ROM and on the Internet. Populations are characterized geographically by social and economic characteristics, and also by housing characteristics. www.census.gov

Methods for Enumerating and Characterizing Populations Exposed to Chemical Substances. Volume 4. U.S. EPA. Presents methods and data sources for identifying and characterizing populations of interest.

APPENDIX C: Summary of Writing SMILES Notations
SMILES: (Simplified Molecular Input Line Entry System)

What is SMILES?

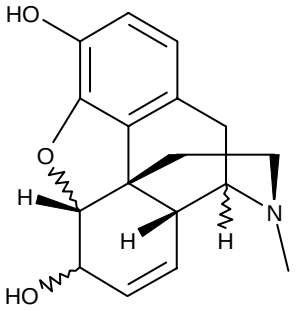
SMILES is "Simplified Molecular Input Line Entry System," which translates a chemical's structure into a string of symbols that is easily understood by computer software. SMILES notation are used to enter chemical structure into EPI Suite™ estimation programs and ECOSAR. Additional examples of SMILES notations are available in the HELP files of EPI Suite™ and ECOSAR. Software programs are available which can translate a chemical structure into SMILES.

References:

Weininger, D. 1988. SMILES, a Chemical and Information System. 1. Introduction to Methodology and Encoding Rules. J. Chem. Inf. Comput. Sci. 28(1): 31-6.
Wiswesser, W.J. 1954. A Line-Formula Chemical Notation. New York: Cromwell.

Why Would I Want to Learn SMILES Notation?

The purpose of SMILES is to translate this 3-dimensional structure below, which is Morphine CAS RN 57-27-2, into a linear representation of the structure so that a computer program can understand the structure.



SMILES Notation for CAS RN 57-27-2 Oc1ccc2CC(N3C)C4C=CC(O)C5Oc1c2C45CC3

Representing Atoms

Atomic symbols and their corresponding SMILES notations:

C	methane (CH_4)
N	ammonia (NH_3)
O	water (H_2O)
P	phosphine (PH_3)
S	hydrogen sulfide (H_2S)
Cl	hydrogen chloride (HCl)

Normally hydrogen is not shown.

Elements must be described in brackets:

[Au]	elemental gold

Representing Bonds

Single, double, triple, and aromatic bonds are represented by the following symbols:

single	–	triple	#
double	=	aromatic	:

Normally single bonds and aromatic bonds do not need to be written in the SMILES notation.

APPENDIX C: Summary of Writing SMILES Notations
SMILES: (Simplified Molecular Input Line Entry System)

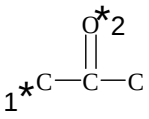
Representing Bonds (continued)

Examples showing bonds are:

CC	ethane (CH_3CH_3)
C=C	ethylene ($CH_2=CH_2$)
COC	dimethyl ether (CH_3OCH_3)
CCO	ethanol (CH_3CH_2OH)
C=O	formaldehyde (CH_2O)
O=C=O	carbon dioxide (CO_2)
O=CO	formic acid (HCOOH)
C#N	hydrogen cyanide (HCN)
[H][H]	molecular hydrogen (H_2)

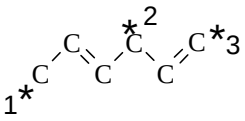
Bonds in Linear Structures

For linear structures, SMILES notation corresponds to conventional diagrammatic notation except that hydrogen can be omitted. Here are two correct ways to represent Acetone CAS RN 67-64-1. The numbered asterisks indicate where on the molecule each SMILES string begins.



valid SMILES:
1. CC(=O)C
2. O=C(C)C

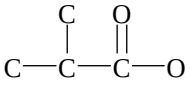
Here are three correct ways to represent 1,4-hexadiene CAS RN 592-45-0. The numbered asterisks indicate where on the molecule each SMILES string begins.



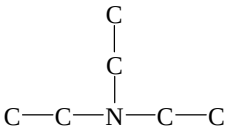
valid SMILES:
1. CC=CCC=C
2. C(C=C)C=CC
3. CC=CCC=C

Representing Branches

Branches are specified by enclosures in parentheses, for example:



CC(C)C(=O)O
Isobutyric acid
CAS RN 79-31-2

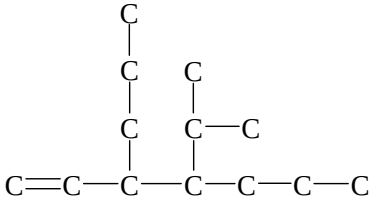


CCN(CC)CC
Triethylamine
CAS RN 121-44-8

Branches also can be nested or stacked, for example:

C=CC(CCC)C(C(C)C)CCC

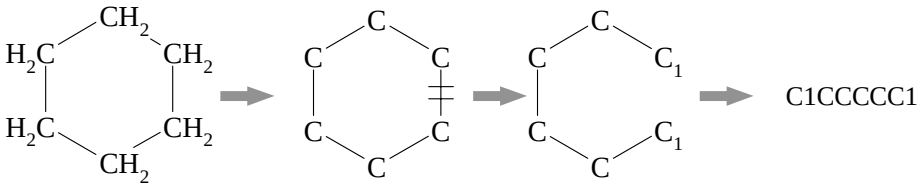
3-propyl 4-isopropyl 1-heptene



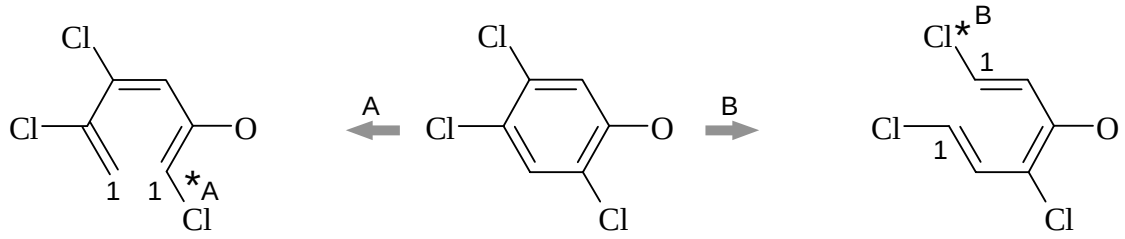
APPENDIX C: Summary of Writing SMILES Notations
SMILES: (Simplified Molecular Input Line Entry System)

Representing Cyclic Structures

Cyclic structures are represented by breaking one single or double (aromatic) bond in each ring. The bonds are numbered in any order, designating ring-opening/closure bonds by a digit immediately following the atomic symbol at each ring closure. This leaves a connected noncyclic graph, which is written as a noncyclic structure by using the three rules described for atoms, bonds, and branches. A typical example is Cyclohexane CAS RN 110-82-7:



Just as in linear structures, there are many different but equally valid descriptions of the same cyclic structure. Many different SMILES notations may be written for the same structure by breaking a ring in different places. For example, here are two valid SMILES notations for 2,4,5-Trichlorophenol CAS RN 95-95-4. The numbered asterisks indicate where on the molecule each SMILES string begins.



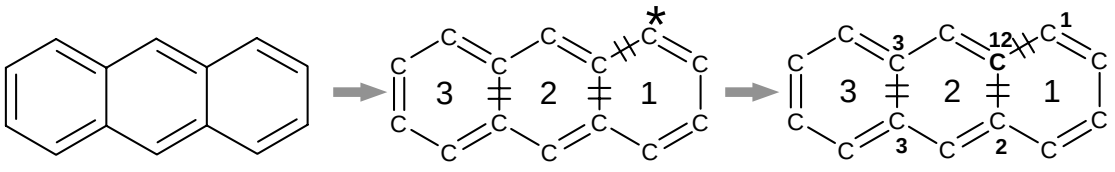
SMILES A
c1(Cl)c(O)cc(Cl)c(Cl)c1

2,4,5-Trichlorophenol
CAS RN 95-95-4

SMILES B
Clc1cc(O)c(Cl)cc1Cl

A single atom may belong to more than one ring and have more than one ring closure. An example of this is Anthracene, in which one atom (bolded below) have more than two ring closures.

Here is the generation of the SMILES notation for Anthracene CAS RN 120-12-7. Number each ring, decide where you want to start the SMILES string (here the SMILES string will begin at the asterisk). Break the rings and give the two atoms at each ring closure the number of that ring.



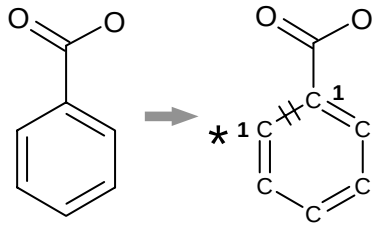
In this example the SMILES notation for Anthracene is: c1cccc2cc3ccccc3cc12

APPENDIX C: Summary of Writing SMILES Notations
SMILES: (Simplified Molecular Input Line Entry System)

Representing Cyclic Structures (continued)

Aromatic structures are distinguished by writing the atoms in the aromatic ring in lower case letters, for example Benzoic acid CAS RN 65-85-0.

Benzoic acid
CAS RN 65-85-0

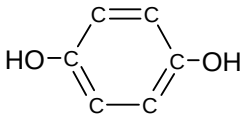


c1ccccc1C(=O)O

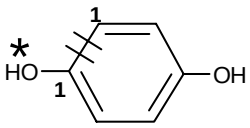
Examples of Aromatic and Nonaromatic Compounds

Of the examples shown on the previous page, Cyclohexane CAS RN 110-82-7, is not aromatic and all carbons are indicated by upper case: C1CCCCC1. Anthracene CAS RN 120-12-7 is aromatic and all carbons are indicated by lower case: c1cccc2cc3ccccc3cc12.

Hydroquinone is **aromatic**. Hydroquinone drawn with aromatic carbons shown in lower case (left) and with aromatic carbons hidden (right).

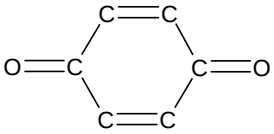


Hydroquinone
CAS RN 123-31-9

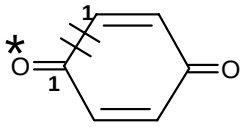


O=c1ccc(O)cc1

Quinone CAS RN 106-51-4 is **nonaromatic**. Quinone drawn with nonaromatic carbons shown in upper case (left) and with nonaromatic carbons hidden (right).



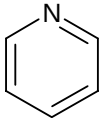
Quinone
CAS RN 106-51-4



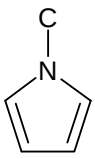
O=C1C=CC(=O)C=C1

Aromatic Nitrogen

Aromatic nitrogens are specified with the aromatic symbol lower case “n” Examples are pyridine and pyrrole:



Pyridine
CAS RN 110-86-1
n1ccccc1

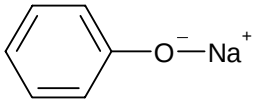


Methyl pyrrole
CAS RN 96-54-8
Cn1ccccc1

APPENDIX C: Summary of Writing SMILES Notations
SMILES: (Simplified Molecular Input Line Entry System)

Disconnected Structures

Disconnected compounds are written as individual structures separated by a period. The order in which ions or ligands are listed is arbitrary. There is no implied paring of one charge with another, and it is not necessary to have a net charge of zero. If desired, the SMILES of one ion may be imbedded in another, as shown in the example the SMILES for Sodium phenoxide.

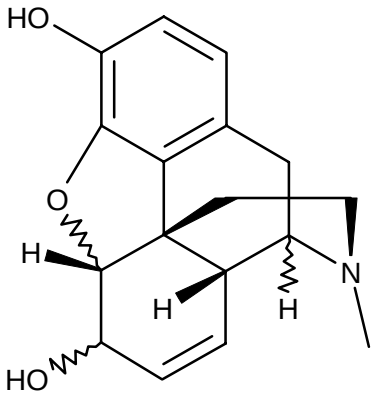


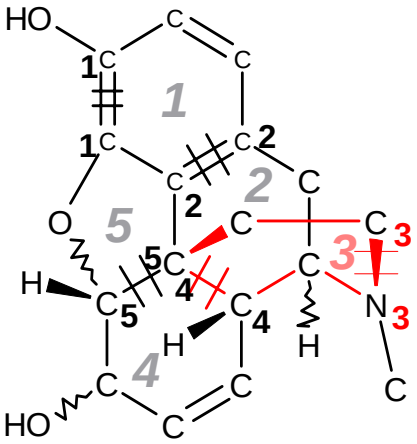
Sodium phenoxide
SMILES Notation

[Na+].[O-]c1ccccc1
or
c1cc([O-].[Na+])ccc1

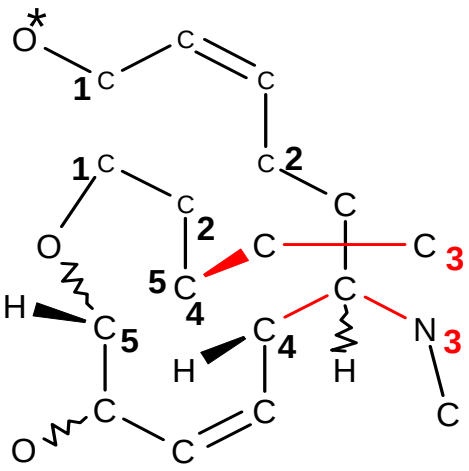
Evolution of SMILES for Morphine

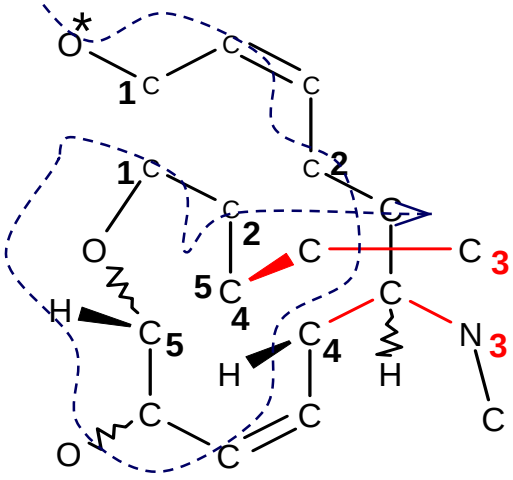
Here is the generation of one correct SMILES notation for Morphine CAS RN 57-27-2.





Number each ring, decide where you want to start the SMILES string (here the SMILES string will begin at the asterisk). Break the 5 rings and give the two atoms at each ring closure the number of that ring. The dashed line indicates the path followed when this SMILES notation was drawn.





In this example the SMILES notation for Morphine is: Oc1ccc2CC(N3C)C4C=CC(O)C5Oc1c2C45CC3

APPENDIX D: Chemicals / Characteristics Related to Local Effects

Chemicals Causing Local Effects

Note: The lists provided here are for illustrative purposes, and are not intended to be comprehensive.

Eye Effects

Chemical properties/considerations relevant to eye effects include:

- Acidity
- Basicity/alkalinity
- Chemical burns (isocyanates, mustards)
- Interaction with proteins (metal salt deposition, quinones, etc.)
- Mechanical abrasions
- Solvent effects
- Surfactancy

Toxicity/irritation/corrosion to the Skin

Irritation Consider:

- Acidity
- Basicity/alkalinity
- Chemical burns
- Lipophilicity
- Mechanical abrasions
- Solvent effects
- Surfactancy

Dermal/Contact Sensitization Consider:

- Electrophilic or nucleophilic groups that could haptenize protein through covalent modification, for example: Aldehydes, ketone, codicils, quinones, other conjugated, unsaturated functional groups, epoxy groups.
- Structural similarities to classes of contact allergens (parent chemical) or impurities belonging to known classes of contact allergens, for example: Antibiotics, Chlorinated antiseptics, Dyes (azo, amine), Formaldehyde releasers, Mercurials, Metals (nickel, chromium, cobalt), Natural products (plant rosins, balsams), and Preservatives.

Photo-toxicity and Photosensitization Consider:

- Chemical structures that are UV absorbing (such as highly conjugated aromatics), for example: Furocoumarins, Polycyclic aromatics, and Porphyrins.
- Structural similarity to systemic agents that cause photoreactions, for example: Non-steroidal anti-inflammatory agents, Sulfonamides, and Tetracyclines.

Local Toxicity to the Gastrointestinal Mucosa Consider:

- Local effects in the G.I. tract will be mediated by solubility, irritation, corrosivity, and local metabolism.
- For irritant and corrosive effects, consider the factors elaborated above for eye and skin.
- For metabolic activation, consider the factors elaborated upon below.

Toxicity to the Respiratory System Consider:

- Irritants that may cause asthma, a disease characterized by (1) airway obstruction that is reversible, (2) airway inflammation, and (3) airway hyperresponsiveness. Classes of compounds that can cause asthma include: Aldehydes, Anhydrides, Isocyanates, and Metals.
- Irritant materials may cause upper airway reactivity (e.g., bronchitis)
- Water soluble, reactive materials (e.g., formaldehyde) may cause nasal or upper airway toxicity an/or irritation
- Particulates and fibers of a particle size that results in deep lung deposition may potentially cause chronic lung injury. Such injury is mediated by inflammatory responses, lung overload, and sustained cell turnover. Examples include: Fibers with a certain length to width ratio (e.g., asbestos), and Particulate dusts (silica, clays, talcs).
- Other classes of respiratory toxicants include: Ammonia and volatile, basic amines, Isocyanates, Metal carbides, Metal oxides, Metal dusts and fumes, Nitrogen oxides, Surfactants, and Transition metals, arsenic, beryllium.

APPENDIX E: Chemical Classes Associated with Systemic Effects

Systemic Toxicity Mediated by Intrinsic Chemical Reactivity or Biotransformation to Reactive Toxicants
Systemic organ toxicity is frequently mediated by the presence of reactive functional groups (whether present in the parent compound or introduced via biotransformation). Reactive compounds or metabolites may exert toxic effects by modification of cellular macromolecules (structural and functional cellular proteins, DNA). This can result in destruction or dysfunction of the target molecules. In addition, covalent modification of target molecules which are covalently modified may render them "foreign" or antigenic (capable of eliciting an immune response). DNA-reactive chemicals have genotoxic potential.

Toxicity Caused by Electrophiles Structural "Red flags" for chemicals containing electrophilic centers include:
- Acyl halides
- Aryl halides
- Azides, – and S-mustards
- Epoxides, strained rings (e.g., sultones)
- Nitroso groups
- Polarized, conjugated double bonds (e.g., quinones, a, ß unsaturated ketones, esters, nitriles)

Functional groups which undergo metabolism to electrophilic centers include:
- Alkyl esters of sulfonic or phosphonic acids
- Aromatic compounds with functional groups that can yield benzylic, aryl carbonium or Nitronium ions
- Aromatic nitro, azo or amine groups
- Conjugated aromatics that undergo epoxidation

Toxicity Caused by Free Radical Formation Compounds which can accept or lose electrons can mediate free radical formation through redox cycling. Structural "Red flags" include:
- Aminophenols
- Catechols, quinines, hydroquinones
- Metal complexes (iron and chromium)
- Peroxides
- Phenothiazines
- Polycyclic aromatics

Systemic Toxicity Associated with Receptor-Mediated Mechanisms Some compounds exert toxicity through substitution for known or unknown tissue receptor ligands. Classes of compounds that could exert toxicity though such mechanisms include:
- Environmental estrogens (putative hormone receptor ligands)
- Fibrates, phthalates (peroxisome proliferator receptor agonists)
- Polychlorinated aromatics (Ah receptor ligands)
- Retinoids (retinoic acid receptor ligands)

<u>Target Organ and Functional Toxicity</u>
Toxicity to the Liver As the primary organ of biotransformation, the liver is susceptible to toxicity mediated by chemical reactivity, as described above. Other agents with toxicity to the liver include:
- Chlorinated hydrocarbons
- Metals, etc.

APPENDIX E: Chemical Classes Associated with Systemic Effects

Toxicity to the Kidney Classes of compounds that are potential nephrotoxins include:
- Amines
- Certain classes of systemic drugs
- Halogenated aliphatic hydrocarbons
- Heavy metals
- Herbicides
- Insoluble salts that precipitate in the kidney (e.g., calcium complexes)
- Mycotoxins
- Organic solvents

Toxicity to the Respiratory System Effects of inhaled respiratory toxicants were addressed above.

Neurotoxicity Chemicals/Classes of compounds which may manifest neurotoxicity include:
- Acids and thioacids
- Arylamide and related substances
- Acrylamides
- Alcohols
- Aliphatic halogenated hydrocarbons
- Alkanes
- Aromatic hydrocarbons
- Carbon disulfide and organic sulfur -containing compounds
- Carbon monoxide
- Catecholamines
- Certain classes of systemic drugs
- Chlorinated solvents
- Cyanide
- Cyclic halogenated hydrocarbons
- Environmental estrogens
- Ethylene oxide
- Gamma-diketones
- Inorganic nitrogenous compounds
- Isocyanates
- Ketones
- Lead
- Mercury compounds
- Metals and metalloids other than mercury and lead
- Nitriles
- Organic nitrogens
- Organophosphates
- Organophosphorus compounds
- Organotins
- Certain Pesticides
- Phenols and related substances
- Phosphorus
- Protein cross-linking agents
- Psychoactive drugs
- Pyridines (e.g., MPTP)

APPENDIX E: Chemical Classes Associated with Systemic Effects

Immunotoxicity (Immunosuppression / Autoimmunity) Classes of compounds which may manifest immunotoxicity include:
- Heavy metals
- Organic solvents
- Certain Pesticides
- Polyhalogenated aromatic hydrocarbons

Genetic Toxicity Classes of compounds that manifest genetic toxicity are often electrophilic agents capable of modifying DNA. Such agents may act as gene mutagens, clastogens or aneugens. Compounds that can intercalate into DNA, free radical generators or chemicals that induce oxidative damage may also act as gene mutagens, clastogens or aneugens.
Mutagenic structural alerts include:
- Acrylates and methacrylates
- Aliphatic or aromatic nitro groups
- Aliphatic or aromatic epoxides
- Alkyl hydrazines
- Alkyl esters of phosphonic or sulfonic acids
- Alkyl aldehydes
- Aromatic ring N-oxides
- Aromatic azo groups
- Aromatic and aliphatic aziridynyl derivatives
- Aromatic alkyl amino or dialkyl amino groups
- Aromatic and aliphatic substituted alkyl halides
- Aromatic amines and N-hydroesters of aromatic amines
- Carbamates
- Chloramines
- Halomethanes
- Monohaloalkanes
- Multiple-ring systems
- N-methylol derivatives
- Nitrogen and sulfur mustards
- Nitroso compounds
- Propiolactones and propiosultones
- Vinyls and vinyl sulfones

Reproductive Toxicity Classes of compounds which may manifest reproductive toxicity include:
- Alcohols
- Alkylating agents
- Chlorinated hydrocarbons
- Certain Fungicides
- Certain Herbicides
- Hydrazines
- Certain Insecticides
- Metals and trace elements
- Nonylphenols
- Plastic monomers
- Solvents (e.g., glycol ethers, benzene, xylenes)
- Steroids or steroid receptor ligands

APPENDIX E: Chemical Classes Associated with Systemic Effects

Developmental Toxicity Classes of compounds which may manifest developmental toxicity include:

- Acrylates
- Androgenic chemicals
- Anilines
- Boron containing compounds
- Chelators
- Chlorobiphenyls
- Compounds which have potential for mutagenicity and oncogenicity
- Epoxides
- Lead
- Lithium
- Mercury
- Nitrogen Heterocyclic compounds
- Phthalates
- Retinoids
- Salicylates
- Short-chain branched carboxylic acid (e.g., valproic acid)
- Small benzenes
- Synthetic steroids (e.g., diethylstibesterol)
- Triazines
- Vinyl groups

Blood Toxicity Classes of compounds which may manifest developmental toxicity include:

- Simple aromatic amines and azo dyes that undergo azo reduction to release aromatic amines

APPENDIX F: High Molecular Weight Polymers

High Molecular Weight Polymers in the New Chemicals Program

From: http://www.epa.gov/opptintr/newchems/hmwtpoly.htm August 2002

There are three categories or types of High Molecular Weight (HMW, >10,000 daltons) polymers typically reviewed by EPA's New Chemicals Program: **(a) soluble**, **(b) insoluble/non-water absorbing ("non-swellable"),** and **(c) water absorbing ("swellable").** EPA has a concern for potential fibrosis of the lung or other pulmonary effects that may be caused by inhalation of respirable particles of water-insoluble HMW polymers. The toxicity may be a result of "overloading" the clearance mechanisms of the lung. EPA also has concerns for water absorbing polymers, based on data showing that cancer was observed in a 2-year inhalation study in rats on a HMW water-absorbing polyacrylate polymer. Each of the three types is treated differently as indicated below:

a. Soluble. EPA does not expect water-soluble polymers to exhibit lung toxicity because they are expected to rapidly clear the respiratory tract and therefore not cause an overloading effect. However, where there is substantial production volume, exposure and release, the Agency will require testing on PMN substances of this type under its exposure-based authority.

b(1). Insoluble: non-water swellable. Although exempt from reporting by the 1995 PMN rule amendments under the polymer exemption criteria, the Agency has concerns for this class of HMW polymers. This concern is based on a study, designated TSCA 8(e)-0668, which reported irreversible lung damage linked with inhalation of respirable particles of water-insoluble polymers (toner used in copy machines) of MW 70,000 or greater. There is a data gap for polymers with MW between 10,000 and 70,000. If a company chooses to submit a PMN for this type of HMW polymer (rather than take advantage of the polymer exemption option), and the PMN substance meets the program's exposure-based criteria (in particular, production volume and inhalation exposure), EPA may regulate under its exposure-based policy with a modified testing scheme. A 90-day subchronic toxicity test via inhalation with a 60-day holding period (absent neurotoxic components and other organ effects) will be triggered under a TSCA Section 5(e) consent order. Data from such a study will be compared to results from 8(e)-0668.

Other references are:

A. Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats. H. Muhle, B. Bellmann, 0. Creutzenberg, C. Dasenbrock, H. Ernst, R. Kilpper, J.C. MacKenzie, P. Morrow, U. Mohr, S. Takenaka, and R. Mermelstein. Fundam. Appl. Toxicol. 17, 280-299(1991).

B. Lung Clearance and Retention of Toner, Utilizing a Tracer Technique During a Long-term Inhalation Study in Rats. B. Bellmann, H. Muhle, 0. Creutzenberg, C. Dasenbrock, R. Kilpper, J.C. MacKenzie, P. Morrow, and R. Mermelstein. Fundam. Appl. Toxicol. 17, 300-313(1991).

C. Chronic Inhalation Study Findings as a Basis for Proposing a New Occupational Dust Exposure Limit. P. Morrow, H. Muhle, and R. Mermelstein. J. American College of Toxicology, 10, No. 2, 279-290(1991).

D. Abstract-Hamster Response to Chronic Test Toner Inhalation. R. Mermelstein, 0. Creutzenberg, C. Dasenbrock, H. Ernst, M. Kuschner, U. Mohr, and H. Muhle. presented at the 1992 Annual Society of Toxicology (SOT) Meeting, Seattle, WA, The Toxicologist (1992). b(2). Insoluble: non-water swellable, highly respirable. Also exempt from reporting under the new polymer exemption. In addition to lung overload described above, these substances raise serious, yet less predictive concerns for potential lung effects associated with their highly respirable size--where a significant percentage of the particles are <10 microns--and lack of absorption potential; the physical effect is deposition to the deep lung and inability to dislodge the particles. For these cases, current Agency policy is to not pursue regulation of the chemical, but to send a letter to the submitter that mentions the basic overload issue from above--with the toner data references--and stresses the heightened concern based on the substance's highly respirable nature--with additional references on "ultrafines," highly respirable particles that are much more toxic to lungs than larger particles of the same material. Such a letter typically will recommend use of a NIOSH-approved respirator or appropriate engineering controls.

APPENDIX F: High Molecular Weight Polymers

General Note on the Insoluble HMW Polymers and the Polymer Exemption. EPA recognizes that there is a different hurdle for placing PMN chemical substances on the TSCA (Toxic Substances Control Act) Inventory than for permitting exemptions for polymers, specified at 40 CFR 723.250. In promulgating this exemption for polymers, EPA generally concluded that "there is an exceedingly low probability that potential exposure to high molecular weight water-insoluble polymers, as a class, will result in unreasonable risk or injury to human health or the environment." (see 60 FR 16322; March 29, 1995). Within the context of individual PMN chemical substances, however, EPA continues to have a concern for the potential for irreversible lung damage when respirable insoluble dusts are inhaled at levels that also produce "lung overloading" and impaired clearance by the lungs. As a result, EPA will assess polymers submitted as PMNs on a case-by-case basis. This concern is based on the above mentioned photocopy toner data (TSCA 8(e)-0668). Based on this concern, EPA reserves the right to require testing under its TSCA exposure-based authority, warranted by high exposures and production volume. In promulgating the polymer exemption in 40 CFR 723.250, EPA did not impose conditions on this category of insoluble high MW polymers as part of the final rule. At the time, EPA stated that, "the Agency believes that manufacturers and users of polymers and chemical substances, in general, where feasible should take appropriate action to mitigate exposure to all respirable particles as part of good industrial hygiene practices." (See 60 FR 16323; March 29, 1995). Accordingly, EPA may send a "letter of concern" to a PMN submitter, as a restatement of this last point. EPA believes such a letter is an appropriate action which fulfills EPA's responsibility to communicate a potential for adverse effects based on the TSCA Section 8(e) photocopy toner data. Note that EPA, in promulgating the 1995 amendments to the Polymer Exemption Rule, elected not to establish an exposure limit for respirable particles, agreeing with public comments that consistency among Federal regulations (i.e., between TSCA new chemicals regulation and OSHA nuisance dust standards) regarding workplace exposure is desirable.

c. Water absorbing (swellable) polymers. For these substances the Agency makes the "may present an unreasonable risk" determination with concerns for fibrosis and cancer, based upon water absorption properties. Concerns are associated with substances that absorb their weight (or greater) in water. The primary reference for Agency concerns for this class of polymers is TSCA 8(e)-1795, submitted by the Institute for Polyacrylate Absorbents (IPA), which indicated that high molecular weight polyacrylate polymers caused lung neoplasms in animal studies. EPA has also reviewed data on modified starches submitted by the Corn Refiners Association, comparing the structures of the test substances with the structures of twelve modified starch PMN substances. You can view the tea-bag protocol (22 Kb PDF) used for this study. Based on the submitted data, EPA was unable to support concerns for the water retentive capacity of these PMN substances as potentially leading to lung cancer. EPA will review future PMNs for modified starches on a case-by-case basis to determine the applicability of these test results to the future PMNs. High molecular weight polymers that swell to twice their weight are not eligible for the polymer exemption. EPA will assess on a case-by-case basis whether these substances pose a risk and whether testing is warranted, and if they are made in substantial amounts and demonstrate potential for acute or chronic worker inhalation exposure.